INHIBITORS OF CYSTATHIONINE-γ-LYASE (CSE), PROPARGYLGLYCINE AND β-CYANOALANINE, MODULATE ARTERIAL VASORELAXATION IN RAT AORTA

Vellecco Valentina, Di Lorenzo Annarita, De Gruttola Luana, Brancaleone Vincenzo, Roviezzo Fiorentina, Bucci Mariarosaria and Cirino Giuseppe

Department of Experimental Pharmacology, Faculty of Pharmacy, University of Naples "Federico II"

Cystathionine-γ-lyase (CSE) is a key enzyme in the tras-sulfuration pathway, which uses L-cysteine to produce hydrogen sulphide (H_2S) in mammalian tissues (1). CSE is a pyridoxal-5'-phosphate-dependent enzyme expressed in the vascular tissues such as rat aorta, tail artery, mesenteric artery and pulmonary arteries (2). It has been shown that reduced biosynthesis of H_2S may contribute to the vasoconstriction associated with both pulmonary and essential hypertension, while excessive formation of this mediator may contribute to the hypotension associated with septic shock (3). Therefore aim of this study was to investigate on the role of CSE/H_2S pathway in vascular tone regulation by using isolated rat aortic rings. Briefly, aorta was harvested from male Wistar rats, cleaned form fat and connective tissues and cut on rings of 2-3 mm and were mounted on isolated organ bath, linked to isometric force transducers.
Two different inhibitors of CSE were used: propargylglycine (PGG), an irreversible "suicide" inhibitor, or β-cyanoalanine (BCA), a reversible inhibitor (4). As expected, in phenylephrine (PE)-precontracted rings, PGG and BCA (1-10 mM) significantly inhibited L-cysteine (1μM-10mM)-induced vasodilatation (max relaxation 64.4±6.2% vs. 76.9±5.2, n=8; $p<0.001$; 54.7±3.6 vs. 76.4±5.3, n=4; $p<0.001$ respectively). However, both CSE inhibitors significantly, and in a concentration manner, inhibited acetylcholine (10nM-30μM)-induced vasorelaxation (max relaxation PGG 65.4±4.3% vs. 86.7±2.5%, n=5; $p<0.001$; max relaxation BCA 58.2±6.2% vs. 84.2±1.5%, n=8; $p<0.001$). Moreover both PGG and BCA reduced SNP-(1nM-1μM) and SNAP-induced vasorelaxation (1nM-3μM), two Nitric Oxide (NO)-donors. PGG treatment did not modify prostacyclin-induced vasorelaxation while it was able to reduce the relaxation induced by YC-1, an NO independent activator of soluble guanylyl cyclase. These results suggest that CSE inhibitors, besides their action on H_2S production, could interfere on NO-mediated vasodilatation.

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